Long-Term Inhalable Particles and Other Air Pollutants Related to Mortality in Nonsmokers

DAVID E. ABBEY, NAOMI NISHINO, WILLIAM F. McDONNELL, RAOUL J. BURCHETTE, SYNNØVE F. KNUTSEN, W. LAWRENCE BEESON, and JIE X. YANG

Loma Linda University, Loma Linda, California; and U.S. Environmental Protection Agency, Research Triangle Park, North Carolina

Long-term ambient concentrations of inhalable particles less than 10 μm in diameter (PM_{10}) (1973–1992) and other air pollutants—total suspended sulfates, sulfur dioxide, ozone (O_3), and nitrogen dioxide—were related to 1977–1992 mortality in a cohort of 6,338 nonsmoking California Seventh-day Adventists. In both sexes, PM_{10} showed a strong association with mortality for any mention of nonmalignant respiratory disease on the death certificate, adjusting for a wide range of potentially confounding factors, including occupational and indoor sources of air pollutants. The adjusted relative risk (RR) for this cause of death as associated with an interquartile range (IQR) difference of 43 d/yr when PM_{10} exceeded 100 $\mu g/m^3$ was 1.18 (95% confidence interval [CI]: 1.02, 1.36). In males, PM_{10} showed a strong association with lung cancer deaths—RR for an IQR was 2.38 (95% CI: 1.42, 3.97). Ozone showed an even stronger association with lung cancer mortality for males with an RR of 4.19 (95% CI: 1.81, 9.69) for the IQR difference of 551 h/yr when O_3 exceeded 100 parts per billion. Sulfur dioxide showed strong associations with lung cancer mortality for both sexes. Other pollutants showed weak or no association with mortality. Abbey DE, Nishino N, McDonnell WF, Burchette RJ, Knutsen SF, Beeson WL, Yang JX. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers.

AM J RESPIR CRIT CARE MED 1999;159:373–382.

There have been three recent prospective cohort studies in the United States of the relationship between long-term ambient concentrations of particulate air pollution and mortality (1–3). The Six Cities Study followed a cohort of 8,111 adults, randomly sampled between 1974 and 1977 from six cities located in the eastern and midwestern United States (1). The American Cancer Society (ACS) Study followed a cohort of 552,138 adults who were enrolled by ACS volunteers throughout the United States and Puerto Rico in 1982 (2). A third study, known as the Adventist Health Study of Smog (AHSMOG Study), has followed a cohort of 6,338 nonsmoking California Seventh-day Adventists (SDAs) since 1977 (3). Two of these studies—the Six Cities Study and the ACS Study—have shown positive associations between long-term concentrations of ambient particles and increased risks of mortality (1, 2). The AHSMOG Study, however, showed no such associations using mortality data from 1977–1987 (3).

Mortality ascertainment has recently been updated on the AHSMOG cohort through 1992. Previously, only indirect estimates of inhalable particles less than 10 μm in diameter (PM_{10}) formed from site- and season-specific regression equations on total suspended particles (TSP) were available (4). Since 1987, PM_{10} has been monitored throughout California. These data have been used to update ambient concentration estimates for study participants using actual monitored PM_{10} through 1992. The purpose of this paper is to study associations between mortality and long-term ambient concentrations of PM_{10} and other air pollutants using the recently updated mortality data through 1992.

METHODS

Questionnaire Data and Follow-up of the Cohort

The study methods have been described in detail previously (5–7). Briefly, 6,338 nonsmoking, non-Hispanic white SDA residents of California were enrolled in 1977. The study participants, ages 27–95 yr at baseline, were part of a larger Adventist Health Study (AHS) (8). Inclusion criteria were the following: having lived 10 yr or longer within 5 miles of their residence at time of enrollment; and residing in one of the three California air basins of San Francisco, South Coast (Los Angeles and eastward), or San Diego, or being part of a 10% random sample of AHS subjects from the remainder of California who met the other inclusion criteria.

All subjects completed a detailed lifestyle questionnaire as part of the AHS in 1976. This questionnaire ascertained anthropometric (height, weight) data, exercise patterns, use of alcohol and tobacco, occupation, current and past dietary habits, parental history of cancer, and history of selected medical conditions (8). Monthly residence and work location histories were obtained for each study subject for the period 1960 through April 1992 or date of death (if subject died prior to April 1, 1992) by using mailed questionnaires (1977, 1987, and 1992), tracing by telephone, and interviewing of surrogates for de-

(*Received in original form June 3, 1998 and in revised form September 17, 1998*)

Although the research described in this article has been funded by the U.S. Environmental Protection Agency, it has not been subjected to Agency review and does not necessarily reflect the view of the Agency. The statements and conclusions in this article are those of the contractor and not necessarily those of the California State Air Resources Board.

Supported by Environmental Protection Agency cooperative agreement CR 819691-02-0 and the California Air Resources Board contract A933-160.

Correspondence and requests for reprints should be addressed to David E. Abbey, Ph.D., Loma Linda University, Center for Health Research, Evans Hall 215, Loma Linda, CA 92350. E-mail: dAbbey@sph.llu.edu

RWLP0259

PM3006519099

Source: https://www.industrydocuments.ucsf.edu/docs/fngj0001

ceased subjects. Only 156 (2.5%) subjects were lost to follow-up. These latter individuals were censored at date of last contact for purposes of inclusion in risk sets. The 1977, 1987, and 1992 questionnaires also contained standardized respiratory symptoms questions, now included as part of the American Thoracic Society questionnaire (9). Computer algorithms were used to classify individuals as to whether they had definite, possible, or no symptoms of asthma, chronic bronchitis, or emphysema (5). The questionnaires also ascertained lifestyle and housing characteristics pertinent to relative exposure to ambient air pollutants as well as indoor sources of air pollutants.

Air Pollution Estimates

Estimates of monthly ambient concentrations of PM_{10}, ozone (O_3), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) were formed for study participants for the period 1966–1992 using fixed site monitoring stations maintained by the California Air Resources Board. For suspended sulfates (SO_4), the time period was 1977–1992 since SO_4 was not monitored in California prior to 1977. The detailed methods for estimating ambient air pollutants for study participants are described elsewhere (4, 6, 10). Briefly, monthly indices of ambient air pollutant concentrations at 348 monitoring stations throughout California were interpolated to zip code centroids according to home or work location histories of study participants, cumulated, and then averaged over time. Interpolations were restricted to zip code centroids within 31.25 miles (50 km) of a monitoring station and were not allowed to cross barriers to air flow or other topographic obstructions in excess of 250 m above the surrounding terrain (6). Quality ratings that reflected the distance of the nearest monitoring station from the zip code centroid were attached to all interpolations in order to allow sensitivity analyses (4, 6).

Concentrations of PM_{10} prior to 1987 were estimated using site- and season-specific regressions based on TSP (4). Since 1987, PM_{10} has replaced TSP as the particulate pollutant monitored throughout California, so monitored PM_{10} data were available for the later years of the study. For PM_{10} and O_3, exceedance frequencies and excess concentrations above several cutoffs were estimated in addition to mean concentrations. Exceedance frequencies were defined as the sum of days above a specified cutoff of PM_{10} and the sum of hours above a cutoff for O_3. The cutoffs used for PM_{10} were 40, 50, 60, 80, and 100 $\mu g/m^3$, denoted by $PM_{10}(40)$, etc. The cutoffs used for O_3 were 60, 80, 100, 120, and 150 parts per billion (ppb). An additional index used for O_3 was the monthly average of the daily 8-h average from 9:00 A.M. to 5:00 P.M. (used to correspond to the usual hours at work locations because separate interpolations were used for work locations). Excess concentration indices were also computed with excess concentration defined as the integrated sum of time × concentration in excess of a cutoff. Correlations of these indices with the exceedance frequency indices were close to one for corresponding cutoffs, so the results are not reported separately for them (6, 11).

Mortality Ascertainment

Deaths during the follow-up period were ascertained using three methods: (*1*) computer-assisted record linkage with the California death certificate files for the years 1977–1992; (*2*) National Death Index files, 1979–1992; and (*3*) our tracing procedures, which included church records. We thus identified 1,628 (989 females, 639 males) study subjects who died. Death certificates were obtained for all of these, and a state-certified nosologist blinded to exposure data coded each death certificate according to the International Classification of Disease, Ninth Revision (ICD9) codes.

Statistical Analysis

Sex-specific adjusted mortality relative risks (RRs) were estimated using Cox proportional hazards regression models. Combined male and female RRs were also estimated, stratifying on sex, when sex-specific models had similar regression coefficients for covariates. Time-dependent proportional hazards models were used that averaged the pollutant from the first monthly value through the month of death. For lung cancer mortality, a 3-yr lag was used, which averaged the pollutant only up to the full 3 yr prior to the month of death because of the expected long latency period between exposure and incidence of cancer. This is the maximum lag time that can be used with the present data, since monthly values prior to 1973 were not stored in the data. The time variable used in the models was survival time from date of enrollment, except for lung cancer mortality, where age on study was used due to the expected lack of short-term effects. Using time on study rather than age as the time variable can bias proportional hazards regression models unless none of the covariates in the models are correlated with age at baseline (12). We found this condition to be met for models in which we used time on study with all correlations having an absolute value less than 0.17. Survival times of participants who did not die were censored at the end of the study period or at the day of last contact if the participant was lost to follow-up. Adjusted RRs were calculated and reported for differences in air pollutant concentrations equal to the interquartile ranges (IQRs) of the 1973–1992 averages of pollutants observed across the study population. Proportional hazard models were stratified if needed to satisfy the proportional hazards assumption. Failure of the proportional hazards assumption was indicated if the statistical significance for change in log likelihood of the fit of the model was less than 0.05 for the cross-product of any variable in the model with the log of the time variable (13).

The following covariates were controlled for in *a priori* models: age at baseline, April 1, 1977; pack-years of past smoking; years lived with a smoker; years worked with a smoker; years of education at baseline; an indicator variable for employment in an occupation with significant exposure to air pollutants for more than 10 yr (14); and body mass index (BMI) measured as (weight in kg)/(height in m)^2. Body mass index was coded as a series of indicator variables to allow for nonlinear relationships with mortality. For lung cancer mortality, the only covariates used were age, pack-years of past smoking, and education due to the small number of cases. Separate Cox proportional hazards models were estimated for the following cause of death categories: all natural cause (ICD9:001–799), cardiopulmonary disease (ICD9:401–440 and 460–519), nonmalignant respiratory disease (ICD9:460–519), and lung cancer (ICD9:162). Only the underlying cause of death was used. An additional outcome used for nonmalignant respiratory disease was any mention of nonmalignant respiratory disease as an underlying or contributing cause of death, subsequently abbreviated CRC mortality. Deaths not in a specific category were censored at time of death. Robustness of the models was evaluated by estimating each model separately for never smokers versus past smokers as well as conducting subgroup analyses for other key variables.

In order to further rule out confounding or effect modification for variables not mentioned above, additional models were developed for those causes of death that showed strong positive associations with pollutants—all natural cause, any mention of nonmalignant respiratory disease, and lung cancer. A large number of potentially confounding or effect-modifying factors, such as medical history, dietary, or other lifestyle factors, were evaluated to be sure their inclusion did not substantially change the pollutant effect estimate. The APPENDIX gives a detailed description of these factors. Those factors were included that substantially changed the pollutant regression coefficient when included or that significantly ($p < 0.05$) improved the fit of the model according to the likelihood ratio criteria (15). A change in the $PM_{10}(100)$ regression coefficient was defined as substantial if it resulted in a change in the RR corresponding to an IQR difference of $PM_{10}(100)$ of more than 0.04. To assure parsimonious models, covariates that did not meet these criteria were dropped. These refined models were used for most results and sensitivity analyses. Regression diagnostics were conducted for all refined models. These regression diagnostics included checks of the proportioned hazards assumption, checks of log linearity for continuous variables, checks for outliers, and stratified analyses. Two-pollutant models were used to evaluate the stability of single-pollutant associations.

RESULTS

Table 1 shows the numbers of sex-specific deaths occurring in the cohort between 1977 and 1992. Descriptive characteristics of the cohort at baseline in 1977 are included for both sexes. Table 2 gives descriptive statistics for ambient air pollutants estimated for study participants averaged 1973 through month of censoring. Table 3 shows adjusted RRs for different causes of mortality. The RRs are calculated for a difference in the

PM3006519100

Source: https://www.industrydocuments.ucsf.edu/docs/fngj0001

TABLE 1

NUMBER OF CAUSE-SPECIFIC DEATHS AND BASELINE (1977) CHARACTERISTICS FOR COHORT (4,060 FEMALES, 2,278 MALES)

Female	Male	
989	639	Total deaths 1977–1992
965	610	All natural cause deaths (ICD9:001–799)
631	398	Cardiopulmonary deaths (ICD9:401–440 and 460–519)
72	63	Nonmalignant respiratory deaths (ICD9:460–519)
246	164	Deaths with any mention of nonmalignant respiratory disease in underlying or contributing cause of death*
12	18	Lung cancer deaths (ICD9:162)
59.2	58.5	Age in years, mean
13.8	36.3	% Smoked in the past
11.3	19.8	Pack-years of smoking, mean for past smokers
47.8	33.8	% Ever lived with smoker
19.9	16.1	Years lived with smoker, mean†
38.2	48.0	% Ever worked with smoker
11.3	15.6	Years worked with smoker, mean†
0.4	10.3	% Occupational exposure to air pollutants for more than 10 yr
13.1	14.3	Years of education, mean
24.6	25.0	Body mass index, (weight in kg)/(height in m)^2, mean
6.4	9.5	% Currently use alcoholic beverages
35.2	44.3	% High total exercise level
9.0	17.5	Hours outdoors per week, mean
33.9	29.8	% Whose father or mother had cancer
32.3	27.6	% High fruit/vegetable consumption‡
46.6	40.0	% High antioxidant vitamin consumption from pills§
33.0	28.8	% Prior heart attack, stroke, diabetes, or high blood pressure

* All death counts except this one are for underlying cause only.
† Mean of non-zero values.
‡ Two or more servings of fruit or fruit juice per day and two or more servings of cooked green vegetables, green salads, or tomatoes per day.
§ At least daily consumption of vitamin A, or more than 1,000 mg vitamin C per week, or 200 U or more vitamin E per week, or 1 or 2 multivitamin pills daily.

IQR of the pollutant across the study population. Table 4 shows RRs for the other covariates in sex-specific refined models for CRC and lung cancer mortality. These were the mortality outcomes showing strong associations with air pollutants. Refined and *a priori* models gave similar results for these outcomes.

All Natural Cause Mortality

For males, PM_{10} showed a significant association with all natural cause mortality, but none of the other pollutants did. When other pollutants were added one at a time to form two-pollutant models with PM_{10}, the PM_{10} coefficient remained stable. When any mention of malignant or nonmalignant respiratory mortality was removed from all natural cause mortality, the RR associated with the IQR difference in PM_{10}(100) dropped from 1.12 to 1.09 (95% confidence interval [CI]: 0.96, 1.23).

For females, none of the pollutants showed a positive association with all natural cause mortality.

Cardiopulmonary Mortality as Underlying Cause

None of the pollutants showed a significant association with cardiopulmonary mortality for either sex.

Nonmalignant Respiratory Mortality as Underlying Cause

None of the pollutants showed a significant association with nonmalignant respiratory mortality for either sex. It was noted that the proportional hazards assumption was not satisfied

TABLE 2

DESCRIPTIVE STATISTICS FOR ESTIMATED AVERAGE AMBIENT AIR POLLUTANT VALUES 1973 TO CENSOR DATE* FOR SUBJECTS

Pollutant	n†	Mean	Standard Deviation	Range‡	Interquartile Range
PM_{10} mean concentration in $\mu g/m^3$	5,963	51.24	16.63	83.93	24.08
Days/year above 100 $\mu g/m^3$ PM_{10}	5,991	31.08	32.48	178.84	42.63
Suspended sulfate (SO_4) mean concentration in $\mu g/m^3$	5,070	7.24	2.55	32.11	2.97
Sulfur dioxide (SO_2) mean concentration in ppb	4,353	5.62	2.81	18.96	3.72
Ozone (O_3) mean concentration in ppb	5,893	26.11	7.65	43.91	12.03
Hours/year above 100 ppb O_3	5,893	329.61	294.51	987.97	551.10
Nitrogen dioxide (NO_2) in ppb	5,652	36.78	12.99	67.87	19.78

Definition of abbreviation: PM_{10} = inhalable particulates less than 10 μm.
* Except SO_4, 1977 to censor date.
† Number of subjects with 80% non-missing data.
‡ Maximum average value − minimum average value with average computed over entire time period. All minimum values were zero so that the ranges presented are maximum values. The zero values were assigned to a few individuals living in pristine areas remote from monitoring stations.

PM3006519101

Source: https://www.industrydocuments.ucsf.edu/docs/fngj0001

TABLE 3

ADJUSTED MORTALITY RELATIVE RISKS AND 95% CONFIDENCE INTERVALS (IN PARENTHESES) BY CAUSE OF DEATH FOR AN INTERQUARTILE RANGE (IQR) DIFFERENCE IN SPECIFIC AIR POLLUTANTS

	Pollutant Average 1973–Censor Date						
	PM_{10} above 100 μg/m³	PM_{10} Mean Conc.	SO_4 Mean Conc.*	SO_2 Mean Conc.	O_3 above 100 ppb	O_3 Mean Conc.	NO_2 Mean Conc.
IQR	43 d/yr	24.08 μg/m³	2.97 μg/m³	3.72 ppb	551.1 h/yr	12.03 ppb	19.78 ppb
Cause of death							
All natural cause							
Males†	1.12**	1.11	1.05	1.05	1.14	1.09	1.03
	(1.01, 1.24)	(0.98, 1.26)	(0.95, 1.16)	(0.94, 1.18)	(0.98, 1.32)	(0.95, 1.25)	(0.91, 1.17)
Females†	0.94	0.94	0.94	1.00	0.90	0.95	0.99
	(0.86, 1.03)	(0.84, 1.04)	(0.86, 1.02)	(0.91, 1.10)	(0.80, 1.02)	(0.85, 1.06)	(0.89, 1.11)
Cardiopulmonary							
Males‡	1.09	1.10	1.05	1.01	1.06	1.08	1.01
	(0.95, 1.24)	(0.94, 1.30)	(0.28, 3.94)	(0.87, 1.18)	(0.88, 1.29)	(0.91, 1.29)	(0.86, 1.19)
Females‡	0.90	0.92	0.97	1.02	0.88	0.97	1.03
	(0.80, 1.01)	(0.80, 1.05)	(0.87, 1.08)	(0.90, 1.15)	(0.75, 1.02)	(0.84, 1.12)	(0.90, 1.18)
Any mention of nonmalignant respiratory							
Males§	1.28**	1.23	1.04	0.87	1.20	1.12	0.87
	(1.03, 1.57)	(0.94, 1.61)	(0.84, 1.29)	(0.68, 1.11)	(0.88, 1.64)	(0.85, 1.47)	(0.67, 1.14)
Females§	1.10	1.10	1.02	0.98	1.01	1.05	0.97
	(0.91, 1.33)	(0.86, 1.40)	(0.84, 1.25)	(0.79, 1.23)	(0.77, 1.33)	(0.82, 1.35)	(0.76, 1.23)
Lung cancer							
Males‖	2.38††	3.36††	—	1.99††	4.19††	2.10	1.82
	(1.42, 3.97)	(1.57, 7.19)		(1.24, 3.20)	(1.81, 9.69)	(0.99, 4.44)	(0.93, 3.57)
Females¶	1.08	1.33	—	3.01††	1.39	0.77	2.81**
	(0.55, 2.13)	(0.60, 2.96)		(1.88, 4.84)	(0.52, 3.67)	(0.37, 1.61)	(1.15, 6.89)

Definition of abbreviations: conc. = concentrations; PM_{10} = inhalable particulates less than 10 μm.

* Averaged 1977–censor date.

† Covariates included age, years of education, pack-years of past smoking, history of high blood pressure, years lived with a smoker, and total exercise level.

‡ Covariates included age, years of education, pack-years of past smoking, years lived with a smoker, years worked with a smoker, occupational exposure for more than 10 yr, and body mass index as two dummy variables with reference category between stated values (< 21.0 or ≥ 27.5 for females, < 22.4 or ≥ 27.3 for males).

§ Covariates included pack-years of past smoking, body mass index as two dummy variables with reference category between stated values (< 21.0 or ≥ 27.5 for females, < 22.4 or ≥ 27.3 for males), total physical exercise, and age within age strata. Models were stratified by age (< 65 versus ≥ 65) and excluded over age 85 in 1977.

‖ Covariates included years of education, pack-years of past smoking, and alcohol use.

¶ Covariates included years of education and pack-years of past smoking.

** $p < 0.05$.

†† $p < 0.01$.

‡‡ $p < 0.001$.

with the *a priori* model. A reduced model that did satisfy the proportional hazards assumption found a positive but nonsignificant association with $PM_{10}(100)$ for males, whose RR for an IQR increase in $PM_{10}(100)$ was 1.15 (95% CI: 0.81, 1.63).

Any Mention of Nonmalignant Respiratory Mortality

Only PM_{10} showed a significant association with any mention of nonmalignant respiratory mortality. Since sex-specific models for this outcome gave similar regression coefficients for PM_{10} and other covariates (Table 4), combined male and female RRs for PM_{10} were also calculated. The combined male and female adjusted RRs of CRC mortality for the IQRs of $PM_{10}(100)$ and PM_{10} mean concentration, respectively, were 1.18 (95% CI: 1.02, 1.36) and 1.16 (95% CI: 0.97, 1.39). Estimation of the RRs for CRC mortality used stratification by age and sex in order to satisfy the Cox proportional hazards assumption. It was necessary to exclude subjects over 85 yr of age in 1977 from the proportional hazards regression models since the proportional hazards assumption could not be satisfied when this older age group was included. No association was observed between CRC mortality and PM_{10} for the 151 male and female subjects over age 85 in 1977. When other pollutants were added one at a time to form two-pollutant models with PM_{10}, the PM_{10} coefficient remained stable or increased.

Lung Cancer Mortality (Males)

In single-pollutant analyses, $PM_{10}(100)$, $O_3(100)$, and SO_2 were all significantly associated with increased risk of lung cancer mortality in males (Table 3). When NO_2 was added with these pollutants in turn to form two-pollutant models, their coefficients remained stable and NO_2 remained nonsignificant. When SO_2 was added to the PM_{10} and O_3 models, all coefficients remained stable, suggesting that the effects of SO_2 are independent of these other pollutants, as is also suggested by the low correlations of SO_2 with other pollutants (Table 5). It was difficult to separate the effects of PM_{10} and O_3 because they were much more highly correlated. In two-pollutant models of $PM_{10}(100)$ and $O_3(100)$, both coefficients remained positive and were reduced in magnitude, with the O_3 coefficient remaining stronger than the PM_{10} coefficient.

Lung Cancer Mortality (Females)

Both SO_2 and NO_2 were significantly associated with increased risk of lung cancer mortality in females (Table 3); however, in a two-pollutant mortality model with SO_2, the NO_2 coefficient became negative, while the SO_2 coefficient remained strongly positive. The SO_2 coefficient also remained stable in two-pollutant models with $PM_{10}(100)$ and $O_3(100)$.

PM3006519102

Source: https://www.industrydocuments.ucsf.edu/docs/fngj0001

TABLE 4

SEX-SPECIFIC ADJUSTED MORTALITY RELATIVE RISKS AND 95% CONFIDENCE INTERVALS (IN PARENTHESES) ASSOCIATED WITH INCREMENTS OF PM_{10}(100) AND OTHER COVARIATES FOR SELECTED MORTALITY OUTCOMES (4,060 FEMALES, 3,778 MALES)

	CRC Mortality*		Lung Cancer Mortality	
Covariate	Females	Males	Females	Males
Number of cases	152*	120*	12	17
43 d/yr when PM_{10} exceeded 100 μg/m³	1.10 (0.91, 1.33)	1.28‖ (1.03, 1.57)	1.08 (0.55, 2.13)	2.38‖ (1.42, 3.97)
5 yr age	1.80# (1.56, 2.08)	2.12# (1.79, 2.52)	**	**
4 yr of education	—	—	0.89 (0.39, 2.00)	0.58 (0.30, 1.11)
10 pack-years of past smoking†	1.14 (0.86, 1.49)	1.20# (1.12, 1.29)	1.41 (0.77, 2.57)	1.39# (1.19, 1.62)
1 unit increase in total exercise level‡	0.86‖ (0.76, 0.98)	0.91 (0.77, 1.09)	—	—
Lowest BMI category§ (females < 21.0, males < 22.4)	1.98# (1.34, 2.94)	1.20 (0.79, 1.83)	—	—
Highest BMI category§ (females ≥ 27.5, males ≥ 27.3)	2.11# (1.44, 3.11)	1.10 (0.66, 1.83)	—	—
Current alcohol use in 1977	—	—	—	3.92‖ (1.35, 11.43)

Definition of abbreviations: BMI = body mass index; CRC = any mention of nonmalignant respiratory mortality in underlying or contributing cause of death; PM_{10} = inhalable particulates less than 10 μm.

* Stratified by age, excluded over age 85 in 1977, age strata were < 65 vs. ≥ 65.

† Mean years since last smoked: 24.5 for females, 28.4 for males.

‡ Four levels: 1 = light/none; 2 = low; 3 = moderate; 4 = high.

§ Reference categories: ≥ 21.0 and < 27.5 for females; ≥ 22.4 and < 27.3 for males.

‖ $p < 0.05$.

# $p < 0.001$.

** Age used as the time variable.

Robustness of Associations for Subgroups

We investigated the robustness of the observed air pollutant associations by conducting subgroup analyses for CRC mortality and lung cancer mortality for the pollutant that had the strongest association with an outcome—PM_{10}(100) for CRC mortality, O_3 for lung cancer mortality in males, and SO_2 for lung cancer mortality in females. The combined sex model was used for CRC mortality.

The association of CRC mortality with PM_{10} was similar in past smokers, RR = 1.23 (95% CI: 0.90, 1.66), and never smokers, RR = 1.17 (95% CI: 1.00, 1.37) for an IQR increase of PM_{10}(100). The associations of lung cancer mortality with O_3 in males were strongly positive for both past smokers, RR = 4.25 (95% CI: 1.50, 12.07), and never smokers, RR = 6.94 (95% CI: 1.12, 43.08), for the IQR of O_3. For female never smokers, an RR of 2.99 (95% CI: 1.66, 5.40) was observed for the IQR of SO_2. There were too few female past smokers to calculate the RR. We did not have a direct measure of years since last smoked for past smokers. However, years since joining the church could be taken as a crude lower bound on this variable. Of past smokers, 7.3% had joined the church less than 5 yr ago and could thus be classified as possible recent past smokers. When these individuals were excluded from analyses, the regression coefficient of PM_{10} for CRC mortality in both males and females and that of O_3 for lung cancer mortality in males became a little larger, and the coefficient for lung cancer mortality and SO_2 in females, 10% smaller. When dummy variables representing years since joining the church (0–16 yr as a reference group, 17–33 yr, and 34–76 yr) were added to the model of CRC mortality and PM_{10}(100) for past smokers, the regression coefficients for PM_{10} and smoke pack-years were within 12% of previous values.

When individuals who reported current use of alcoholic beverages at baseline (6.4% of females and 9.5% of males) were excluded, stronger associations were observed for PM_{10}(100) with CRC mortality, O_3(100) with lung cancer mortality in males, and SO_2 with lung cancer mortality in females.

For 2,680 subjects who reported low antioxidant vitamin consumption at baseline, the RR for CRC mortality for an IQR difference of PM_{10} was 1.26 (95% CI: 1.01, 1.57), while the RR for 2,326 subjects with high antioxidant vitamin consumption was 1.08 (95% CI: 0.89, 1.32). For lung cancer mortality, there were too few cases to conduct subgroup analyses.

For subjects who reported a prior heart attack, stroke, diabetes, or high blood pressure at baseline, the association of PM_{10} with CRC mortality was similar to those who did not report these events. In 1977, subjects were classified as to whether they had definite symptoms of asthma, chronic bron-

TABLE 5

CORRELATIONS BETWEEN LONG-TERM AVERAGES OF POLLUTANTS ESTIMATED FOR STUDY PARTICIPANTS, 1973 THROUGH MONTH OF CENSORING (EXCEPT SO_4, ONLY SINCE 1977)

	PM_{10} mc	Ozone (100)	Ozone mc	SO_4 mc	SO_2 mc	NO_2 mc
PM_{10}(100)	0.85	0.84	0.63	0.33	−0.05	0.15
PM_{10} mc	1.00	0.83	0.77	0.68	0.31	0.56
Ozone 100	—	1.00	0.78	0.43	0.13	0.41
Ozone mc	—	—	1.00	0.53	0.09	0.36
SO_4 mc	—	—	—	1.00	0.68	0.76
SO_2 mc	—	—	—	—	1.00	0.79

Definition of abbreviations: PM_{10} = inhalable particulates less than 10 μm; mc = mean concentration; PM_{10}(100) = d/yr when PM_{10} exceeded 100 μg/m³; ozone (100) = h/yr when ozone exceeded 100 ppb.

* Number of subjects having at least 80% nonmissing monthly values for both pollutants varies from 4,150 to 5,963.

PM3006519103

Source: https://www.industrydocuments.ucsf.edu/docs/fngj0001

chitis, or emphysema (5). The presence of these respiratory symptoms in 1977 increased the risk of death from respiratory-associated causes to 1.49 (95% CI: 1.12, 1.99). Subjects classified as having definite respiratory symptoms in 1977 showed a similar association of PM_{10} with CRC mortality to those without such symptoms.

Subjects were stratified into three groups according to hours per week spent outdoors as reported at baseline: low was classified as 4 h/wk or less, medium as greater than 4 but less than or equal to 16 h/wk, and high as more than 16 h/wk. The RRs of CRC mortality for the IQR of $PM_{10}(100)$ for each of these groups were: low, RR = 1.07 (95% CI: 0.85, 1.34); medium, RR = 1.18 (95% CI: 0.90, 1.55); and high, RR = 1.31 (95% CI: 1.02, 1.68).

When subjects were restricted to those living in high population density areas (> 10 homes within a quarter-mile radius), results were similar to those reported for PM_{10} and CRC mortality in both sexes. For lung cancer mortality in males, the RR as associated with elevated O_3 was higher. This was true for PM_{10} as well.

Potentially Confounding Factors

A large number of lifestyle and other potentially confounding factors of PM_{10} were evaluated in this study (Table 1 and APPENDIX). None of these potentially confounding factors, when added one at a time to the PM_{10} mortality models, substantially changed the PM_{10} coefficient, except possibly for factors already included in refined models; thus, adjustments for these factors were not needed. We defined a substantial change in the $PM_{10}(100)$ regression coefficient as one that would result in a change of more than 0.04 in the RR corresponding to an IQR difference of $PM_{10}(100)$. The effects on the PM_{10} coefficient of the potential confounders that were included in the refined sex combined CRC mortality model were as follows. For a basic model stratified by sex and age and including only age as a covariate, the RR of CRC mortality for an IQR increase in $PM_{10}(100)$ was 1.10 (95% CI: 0.97, 1.25); when smoke pack-years were added, the RR was 1.14 (95% CI: 1.00, 1.30); when the BMI indicator variables were also added, the RR was 1.18 (95% CI: 1.02, 1.35); with total exercise scale added to the above variables in the model, the RR was 1.18 (95% CI: 1.02, 1.36).

To further evaluate potential confounding, we conducted stratified analysis for any potential confounders that showed a strong association with PM_{10} and a stronger positive association with CRC mortality than PM_{10}. An association of a potential confounder with PM_{10} was deemed "strong" for a continuous variable if the absolute value of the correlation coefficient with $PM_{10}(100)$ was greater than 0.20. For categorical variables, an association was deemed "strong" if the p value of a one-way analysis of variance of $PM_{10}(100)$ across the categories was less than 0.10. An association of a potential confounder with CRC mortality was deemed stronger than that for $PM_{10}(100)$ if the magnitude of the RR for the potential confounder exceeded the RR for the IQR increase of $PM_{10}(100)$. For continuous valued potential confounders, we evaluated the RR for an IQR increase: for categorical potential confounders, we evaluated the RR with reference to the lowest or highest category. Based on these criteria, stratified analyses were conducted for both sexes; occupational exposures to air pollutants for more than 10 yr, current alcohol consumption (yes, no), vitamin C intake, multivitamin intake, a salad index, and several meat indices. In the stratified analyses, we evaluated the RR of CRC mortality as associated with the IQR increase of $PM_{10}(100)$ within each stratum of the confounding factor. The RRs were consistent with those reported above for the entire group of subjects, except for some small subgroups, suggesting that no confounding was present. For each factor evaluated, CIs for all subgroups overlapped each other. A similar evaluation of potential confounders was done for O_3 and lung cancer mortality for males. Again no evidence of confounding was found. Although we evaluated a large number of potential confounders, we cannot rule out the possibility of confounding by unmeasured variables.

Possible Underreporting of Current Smoking

All reported current smokers in 1977 were excluded from all analyses. However, since smoking is a religious proscription of the SDA Church, it is possible that current smoking was underreported. This could bias our observed associations between long-term ambient concentrations of air pollutants and respiratory-related mortality (16). Using the reported current smoking rates in our cohort in 1977 (1.1% for females, 2.2% for males), we conducted sensitivity analyses, assuming a 10-fold greater risk for current smokers and 50% underreporting, which was (*1*) nondifferential and then (*2*) differential with respect to air pollution exposure. For case (*2*), we assumed that underreporting occurred in the top quartile of air pollution exposure, but not in the other quartiles. Our sensitivity analyses indicated that the RRs reported in Table 3 would underestimate the true RR for the case of nondifferential underreporting and would overestimate the true RRs by not more than 15% of the true RR for the case of differential underreporting.

Cutoffs

The relationship between CRC mortality in both sexes and PM_{10} was evaluated for other cutoffs—40, 50, 60, and 80 $\mu g/m^3$. Exceedance frequencies for cutoffs of 60 $\mu g/m^3$ and higher showed statistically significant associations with CRC mortality. A similar evaluation for lung cancer mortality in males and the different cutoffs of O_3 showed all cutoffs of 60–150 ppb as well as the 8-h average to be significantly associated with lung cancer mortality, but not the 24-h average of O_3.

Time Trends

Except for O_3 mean concentration, levels of all pollutants and pollutant indices used in this study declined from 1973 to 1992, or 1977 to 1992 in the case of SO_4. Ozone mean concentration stayed about the same, though exceedances above 100 ppb O_3 declined. The most marked decline was seen for SO_2 mean concentration, which dropped from an annual average of 11.1 ppb in 1973 to 1.1 ppb in 1991, the last complete year of follow-up. Declines in other pollutant indices were much less marked, and most of the cohort experienced many exceedances for the exceedance frequency indices, even in the later years of the study. For example, in 1991, two-thirds of the cohort experienced one or more months when PM_{10} exceeded 100 $\mu g/m^3$.

To determine if the elevated risks of CRC mortality as associated with $PM_{10}(100)$ might be due mainly to levels experienced early in the time period, the proportional hazards regression was rerun using a moving average of $PM_{10}(100)$ averaged for 4 yr prior to the risk set. The RR for an IQR increase decreased slightly: RR = 1.15 (95% CI: 1.00, 1.32).

Time Spent Indoors

We reran refined models using adjusted outdoor ambient concentrations obtained by applying an indoor/outdoor adjustment factor to mean estimated ambient concentrations according to time spent indoors as reported by season for each study participant in 1977. Indoor adjustment factors of 0.7 for PM_{10}, 0.5 for O_3, and 0.6 for SO_2 were used (17). For NO_2, in-

PM3006519104

Source: https://www.industrydocuments.ucsf.edu/docs/fngj0001

door sources were not measured until 1987; hence, adjusted NO_2 could not be used in mortality analyses (10). The results of using adjusted ambient concentration were consistent with those reported for unadjusted mean concentrations of PM_{10} with CRC mortality in both sexes, O_3 with lung cancer mortality in males, and SO_2 with lung cancer mortality in males and in females.

Restriction of Distance from Monitoring Station

All interpolations were restricted to be within 31.25 miles of a monitoring station. We conducted sensitivity analyses by further restricting subjects to those who lived at least 80% of their months within 10 miles of a monitoring station for PM_{10} or within 20 miles of a monitoring station for O_3. These were distances deemed by the Environmental Protection Agency (EPA) to be acceptable quality for interpolation (6). Approximately 63% of subjects met these criteria for PM_{10} and 87% for O_3. When analyses were restricted to these subgroups, the RRs relating CRC mortality in both sexes with PM_{10} and lung cancer mortality in males with O_3 were within 6% of previous values. The RR of lung cancer mortality with PM_{10} was 20% smaller for males.

Comparison of Current with Previous Findings from This Cohort

Previous published findings from analyses on this cohort showed no associations between all natural cause mortality and air pollutants during the first 10 yr of follow-up, whereas present analyses using 15 yr of follow-up do show associations (3). Combined male and female RRs of 1.0 or slightly less were observed previously. The particulate pollutant used previously was days per year in excess of 200 $\mu g/m^3$ of TSP (TSP[200]). We used TSP(200) averaged over the baseline period 1973–1977 and compared the sex-specific regression coefficients of TSP(200) as associated with all natural cause mortality for 10 yr of follow-up versus 15 yr (1977–1992). The regression coefficients for the two time periods were in close agreement. Similar results were obtained for PM_{10}(100). When the model used previously was rerun and sex-specific RRs were calculated for an IQR of TSP(200) of 33 d/yr, we observed RRs of 1.13 (95% CI: 0.97, 1.31) for males and 0.91 (95% CI: 0.80, 1.04) for females. From Table 3, we see that current sex-specific results for PM_{10} were very close to these. Sex-specific results were not presented previously for all natural cause mortality since we had not at that time noticed the marked differences between sexes in exposure due to males spending considerably more time outdoors than females. Further discussion of discrepancies between sexes is given below.

DISCUSSION

Summary

In this report, we have found long-term ambient concentrations of PM_{10} to be associated with increased risks of all natural cause mortality in males, mortality with any mention of nonmalignant respiratory causes in both sexes, and lung cancer mortality in males. Long-term ambient concentrations of O_3 were even more strongly associated with increased risk of lung cancer mortality in males, and SO_2 was independently associated with increased risk of lung cancer mortality in both males and females.

In reporting observed associations between specific causes of death and individual monitored pollutants, we realize that differences could be due to measurement error and that some of the observed effects could be the result of correlations among pollutants. Also, we were limited to pollutants that had been widely monitored over long time periods and recognize that the true toxic agent may not have been monitored.

New Results versus Six Cities and ACS Studies

Comparisons of current results with published findings from the Six Cities and the ACS Studies are somewhat limited because updated estimates of fine particles less than 2.5 μm in diameter ($PM_{2.5}$) are not yet available on our cohort. The ACS Study has published results only pertaining to $PM_{2.5}$ and SO_4 (2). Although the Six Cities Study addressed all of the pollutants that we have addressed, their ability to differentiate between specific pollutants was limited due to only having six different air pollution sites, those of the six cities. Also, there may have been an inadequate range of O_3 across these cities to show effects of O_3 (1). We compare our results by cause of death below with the other two long-term prospective studies that have measured respirable particles. For ease of comparison with our results given in Table 3, we have converted RRs cited by the other studies to correspond to IQR increases used in our study. For the sake of abbreviation, it will be understood that all the RRs cited below are for the IQR increases given in Table 3. Results from the Six Cities Study were not given sex-specific by pollutant. Comparisons with older studies that did not measure respirable particles or with cross-sectional studies will not be made. These studies were thoroughly reviewed in the EPA particulate criteria document (18). Most studies show positive associations between long-term ambient levels of particulate pollutants and mortality.

All Natural Cause Mortality

The Six Cities Study showed associations between all natural cause mortality and PM_{10}, $PM_{2.5}$, and SO_4. The RRs for mean concentrations of PM_{10} and SO_4 were 1.23 (95% CI: 1.07, 1.40) and 1.09 (95% CI: 1.03, 1.15), respectively. The ACS Study showed associations between all natural cause mortality and $PM_{2.5}$ and SO_4. The RR for SO_4 mean concentration for males was 1.02 (95% CI: 1.01, 1.03) and for females was 1.03 (95% CI: 1.01, 1.04). Our associations of all natural cause mortality with PM_{10} and SO_4 for males were positive but smaller than for the Six Cities Study and were negative for females. Our observed RR for SO_4 for males was larger than that observed in the ACS Study.

Cardiopulmonary Mortality

Both the Six Cities and the ACS studies showed positive associations between cardiopulmonary deaths and pollutants studied. The Six Cities Study did not give pollutant-specific RRs for specific causes of death but only the RRs for the most versus the least polluted city. The RR for the most versus the least polluted city was 1.37, somewhat larger than the RR we observed for males for PM_{10}. The difference in PM_{10} between the most and the least polluted cities was 28.3 $\mu g/m^3$ (comparable to our IQR); that for SO_4 was 7.5 $\mu g/m^3$ (considerably more than our IQR). The ACS Study gave an RR for SO_4 for males of 1.03 (95% CI: 1.01, 1.04) and for females of 1.05 (95% CI: 1.03, 1.07). Our data showed a positive association for SO_4 comparable to the ACS Study for males but negative associations for PM_{10} and SO_4 for females (Table 3).

Any Mention of Nonmalignant Respiratory (CRC) Mortality

Any mention of nonmalignant respiratory disease as an underlying or contributing cause of death was not studied in the other two studies. Our data showed only PM_{10} to have a strong association with this outcome for both sexes that re-

PM3006519105

Source: https://www.industrydocuments.ucsf.edu/docs/fngj0001

mained strongly positive when other pollutants were added one at a time in two-pollutant models.

Nonmalignant Respiratory Disease as Underlying Cause of Death

This cause of death as an underlying (not contributing) cause of death was considered in the Six Cities Study, but not the ACS Study. The Six Cities Study found no association with any pollutant (1). We found a positive, though nonsignificant, association with PM_{10} in males with an RR of 1.15 (95% CI: 0.81, 1.63). This nonsignificant result may be due to inadequate power since there was a small effect and small number of cases for this outcome.

Lung Cancer Mortality

The Six Cities Study showed an RR for lung cancer mortality for the most polluted versus the least polluted city of 1.37 (95% CI: 0.81, 2.31). For our IQR of SO_4, the ACS Study gave an RR for males of 1.43 (95% CI: 1.13, 1.81) and for females of 1.17 (95% CI: 0.80, 1.72). The ACS Study also showed positive associations between lung cancer mortality and $PM_{2.5}$. However, these associations became negative in never smokers for both sexes. Our data showed a positive association between PM_{10} and lung cancer mortality for females, and our strongest association of PM_{10} was with lung cancer mortality in males, which remained positive and strong in never smokers. This association also remained positive and strong in two-pollutant models with other pollutants. Because of inadequate lag time, SO_4 has not been studied in our data with respect to this outcome, SO_4 data being only available since 1977 in California. However, SO_2 was significantly associated with increased risk of lung cancer mortality in both sexes, and the effects remained stable in two-pollutant models with other pollutants. Long-term averages of SO_2 and SO_4 were fairly highly correlated in our cohort. Ambient levels of O_3 above 100 ppb were more strongly associated with lung cancer mortality in males than were any of the other pollutants, but this was not true for females. The Six Cities Study lacked the high levels of O_3 experienced in Southern California; the ACS Study did not study O_3.

Differences between Sexes

Findings were consistent between sexes for the other two studies. This was only true in our cohort for associations between PM_{10} and CRC mortality and between SO_2 and lung cancer mortality. Notable differences between males and females were observed for lung cancer mortality as associated with PM_{10} and O_3, where males showed much stronger associations than females. Males in our study spent significantly more time outdoors than females, and stronger associations of PM_{10} with CRC mortality were observed for males who spent more time outdoors. Thus, differences between males and females in exposure to ambient pollutants may partially explain these discrepancies (14). We also noted several differences between males and females in exposures to other pollutants, such as tobacco smoke and occupational sources (Table 1). There may be other reasons for the observed differences, and this needs to be explored further in future research with a larger number of cases. Future research on this cohort pertaining to $PM_{2.5}$ may find fewer discrepancies between sexes since indoor and outdoor levels of $PM_{2.5}$ tend to correlate highly (2), thus diminishing differences between sexes in exposure due to males spending more time outdoors.

Tobacco Smoke Exposure

Though the effects of tobacco smoke exposure were significant for males, the effects were small in this cohort. This may be because no reported current smokers were included in analyses and the average length of time since past smokers had last smoked, estimated from age of joining the church, was 27 yr. Only 7.3% of past smokers could be classified as possibly smoking within the past 5 yr.

Results of this study suggest that the associations between air pollutants and mortality (both CRC and lung cancer) are not due to inadequate control of tobacco smoke exposure because of the following reasons: (*1*) the associations persisted in stratified analysis of past smokers and never smokers and remained similar when pack-years of past smoking were controlled for as well as when dummy variables were used to represent past smoking and estimated years since last smoked; and (*2*) the associations persisted in models that controlled for years worked with a smoker and years lived with a smoker. It is unlikely that underreporting of current smoking could account for the observed associations, since our sensitivity analyses indicated that if underreporting were nondifferential, our reported RRs would underestimate the true RR. Even if underreporting were differential, reported RRs would overestimate the true RR by not more than 15%. We have no reasons to suspect differential underreporting in this cohort.

Respiratory Disease and Mortality

The positive association we have observed between death with any mention of nonmalignant respiratory disease and PM_{10} is consistent with earlier findings on this cohort, which observed increased prevalence of asthma, chronic bronchitis, or emphysema in 1977 with long-term ambient concentrations of TSP (19). In current analyses, prevalence of these respiratory symptoms in 1977 was found to be a very strong predictor of CRC mortality. Recently published analyses pertaining to PM_{10} and respiratory disease on this cohort showed PM_{10} to be related to development of overall respiratory symptoms and chronic productive cough (4, 20). Elevated long-term concentrations of PM_{10} were also found to be associated with decrements in lung functions for males, especially those whose parents had asthma, chronic bronchitis, emphysema, or hay fever, and with increased peak expiratory flow lability in both sexes (21). Particulate pollutants have also been found to be associated with asthma, chronic bronchitis, and emphysema as well as decrements in lung function in cross-sectional data from U.S. cities (22–24).

Measurement Error

We have unknown amounts of measurement error in both the estimated long-term ambient concentrations of pollutants as well as other covariates. This could bias our estimates of pollutant regression coefficients. One source of measurement error is that due to interpolating ambient concentrations from fixed site monitoring stations to zip code centroids of work and home locations of study participants. When cumulated over a 2-yr period, correlations between interpolated and actual monitored values of mean concentration were high—0.88 for PM_{10}, 0.87 for O_3, 0.84 for SO_4, 0.64 for SO_2, and 0.92 for NO_2 (4, 7, 25, 26). When analyses were restricted to subjects living at least 80% of their months within distances of a monitoring station deemed by the EPA to have an acceptable quality of interpolation, results consistent with those reported above without restriction were obtained. Another source of measurement error is our use of indirect estimates of PM_{10} prior to 1987 when monitored PM_{10} first became widely available throughout the state of California. During a 2-yr period, both PM_{10} and TSP were consistantly monitored at a number of stations throughout California, and these data were used to identify site- and season-specific regression equations from which

PM3006519106

Source: https://www.industrydocuments.ucsf.edu/docs/fngj0001

PM_{10} concentrations could be predicted from TSP concentrations (4). For this 2-yr period, we evaluated the precision of our interpolation algorithms for predicting PM_{10} concentrations at each monitoring site using the PM_{10} measurements from the surrounding monitoring sites and also using the PM_{10} values estimated from the TSP measurements from the same surrounding monitoring sites. The correlation between measured mean PM_{10} and interpolated mean PM_{10} was 0.88 and 0.86, respectively, using measured PM_{10} and PM_{10} estimated from TSP values from the surrounding monitoring sites. The correlation between measured $PM_{10}(100)$ and interpolated $PM_{10}(100)$ was 0.79 and 0.67, respectively, using measured PM_{10} and PM_{10} estimated from TSP values from the surrounding sites. This indicates that use of TSP to predict mean PM_{10} resulted in minimal loss of precision compared with use of measured PM_{10}. Use of TSP as a predictor for $PM_{10}(100)$, however, for the years prior to 1987 resulted in some additional measurement error. The consistency in our findings regarding health effects of the different indices of PM_{10} suggests that this source of measurement error may not be seriously affecting our results.

Use of Ambient Concentration Estimates for Pollutants

An important limitation of assessing associations between long-term ambient concentrations of air pollutants and mortality is that our estimates are of outdoor ambient concentrations, not personal exposure. We have dealt with the lack of personal exposure measurements in two ways: (*1*) by offering self-reports of personal exposure to other sources of particles, such as past smoking, passive smoking, occupational, etc., as covariate candidates for the health effects models; and (*2*) by adjusting mean ambient concentrations of all pollutants according to time spent indoors. The results of using adjusted ambient mean concentrations were consistent with those reported for unadjusted mean concentrations.

Conclusions and Future Research Needed

Our results indicate that long periods of residence and work location in areas of high ambient air pollution are associated with increased mortality. We observed associations of PM_{10} with all natural cause mortality in males and with nonmalignant respiratory mortality in both sexes. Lung cancer mortality was associated with PM_{10} and O_3 in males and with SO_2 in both males and females. These results do not appear to be due to confounding by any of a large number of measured risk factors in this cohort of nonsmoking California adults.

Although findings of the relationship between PM_{10} and mortality from our study are qualitatively in agreement with those from the Six Cities and ACS Studies, the discrepancies among these studies reported above, with respect to specific particulate pollutants and specific causes of mortality, need to be further explored (1, 2). This would require updating $PM_{2.5}$ estimates for our cohort and adding other pollutants to the ACS Study, as well as studying contributing nonmalignant respiratory causes of death for the other two studies.

Acknowledgment: The writers acknowledge the helpful assistance of Beverley Stocker for word processing. The writers thank Michael D. Lebowitz, Ph.D., for his helpful suggestions throughout the course of this study and in preparation of this manuscript. The writers also thank Dane Westerdahl, John Moore, and Andy Alexis of the California Air Resources Board for providing the air quality data.

References

1. Dockery, D. W., C. A. Pope, III, X. Xu, J. D. Spengler, J. H. Ware, M. E. Fay, B. G. Ferris, Jr., and F. E. Speizer. 1993. An association between air pollution and mortality in six U.S. cities. *N. Engl. J. Med.* 329:1753–1759.
2. Pope, C. A., III, M. J. Thun, M. M. Namboodiri, D. W. Dockery, J. S. Evans, F. E. Speizer, and C. W. Heath, Jr. 1995. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am. J. Respir. Crit. Care Med.* 151:669–674.
3. Abbey, D. E., P. K. Mills, F. F. Petersen, and W. L. Beeson. 1991. Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-day Adventists. *Environ. Health Perspect.* 94:43–50.
4. Abbey, D. E., B. L. Hwang, R. J. Burchette, T. Vancuren, and P. K. Mills. 1995. Estimated long-term ambient concentrations of PM_{10} and development of respiratory symptoms in a nonsmoking population. *Arch. Environ. Health* 50:139–152.
5. Hodgkin, J. E., D. E. Abbey, G. L. Euler, and A. R. Magic. 1984. COPD prevalence in nonsmokers in high and low photochemical air pollution areas. *Chest* 86:830–838.
6. Abbey, D. E., J. Moore, F. Petersen, and L. Beeson. 1991. Estimating cumulative ambient concentrations of air pollutants: description and precision of methods used for an epidemiological study. *Arch. Environ. Health* 46:281–287.
7. Mills, P. K., D. Abbey, W. L. Beeson, and F. Petersen. 1991. Ambient air pollution and cancer in California Seventh-day Adventists. *Arch. Environ. Health* 46:271–280.
8. Beeson, W. L., P. K. Mills, R. L. Phillips, M. Andress, and G. E. Fraser. 1989. Chronic disease among Seventh-day Adventists, a low-risk group: rationale, methodology, and description of the population. *Cancer* 64:570–581.
9. American Thoracic Society. 1995. Standardization of spirometry: 1994 update. *Am. J. Respir. Crit. Care Med.* 152:1107–1136.
10. Abbey, D. E., S. D. Colome, P. K. Mills, R. Burchette, W. L. Beeson, and Y. Tian. 1993. Chronic disease associated with long-term concentrations of nitrogen dioxide. *J. Expo. Anal. Environ. Epidemiol.* 3: 181–202.
11. Abbey, D. E., M. D. Lebowitz, P. K. Mills, F. F. Petersen, W. L. Beeson, and R. J. Burchette. 1995. Long-term ambient concentrations of particulates and oxidants and development of chronic disease in a cohort of nonsmoking California residents. *Inhalation Toxicology* 7:19–34.
12. Korn, E. L., B. I. Graubard, and D. Midthune. 1997. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am. J. Epidemiol.* 145:72–80.
13. Kleinbaum, D. G. 1996. Survival Analysis: A Self-Learning Text. Springer-Verlag, New York. 152–155.
14. Greer, J. R., D. E. Abbey, and R. J. Burchette. 1993. Asthma related to occupational and ambient air pollutants in nonsmokers. *J. Occup. Environ. Med.* 35:909–915.
15. Maldonado, G., and S. Greenland. 1993. Simulation study of confounder-selection strategies. *Am. J. Epidemiol.* 138:923–936.
16. Shapiro, S., J. V. Castellana, and J. M. Sprafka. 1996. Alcohol-containing mouthwashes and oropharyngeal cancer: a spurious association due to underascertainment of confounders. *Am. J. Epidemiol.* 144:1091–1095.
17. Winer, A. M., F. W. Lurmann, L. A. Coyner, S. D. Colome, and M. P. Poe. 1989. Characterization of air pollution exposures in the California South Coast Air Basin: application of a new regional human exposure (REHEX) model. *In* Final Report, Contract No. TSA 106-01-88, South Coast Air Quality Management District, Statewide Air Pollution Research Center, University of California, Riverside, CA. 33–47.
18. U.S. Environmental Protection Agency. 1996. Air Quality Criteria for Particulate Matter, Vol. 3. U.S. Environmental Protection Agency, Research Triangle Park, NC. 134-183. Publication No. PB96-168257 EPA/600/P-95/001CF.
19. Euler, G. L., D. E. Abbey, A. R. Magie, and J. E. Hodgkin. 1987. Chronic obstructive pulmonary disease symptom effects of long-term cumulative exposure to ambient levels of total suspended particulates and sulfur dioxide in California Seventh-day Adventist residents. *Arch. Environ. Health* 42:213–222.
20. Abbey, D. E., N. Nishino, and W. F. McDonnell. 1998. Development of chronic productive cough as associated with long-term ambient inhalable particulate pollutants (PM_{10}) in nonsmoking adults: the Adventist health study of smog. *Applied Occupational and Environmental Hygiene* 13:444–452.
21. Abbey, D. E., R. J. Burchette, S. F. Knutsen, W. F. McDonnell, M. D. Lebowitz, and P. L. Enright. 1998. Long-term particulate and other air pollutants and lung function in nonsmokers. *Am. J. Respir. Crit. Care Med.* 158:289–298.
22. Schwartz, J. 1993. Particulate air pollution and chronic respiratory disease. *Environ. Res.* 62:7–13.
23. Chestnut, L. G., J. Schwartz, D. A. Savitz, and C. M. Burchfiel. 1991. Pulmonary function and ambient particulate matter: epidemiologic

PM3006519107

Source: https://www.industrydocuments.ucsf.edu/docs/fngj0001

evidence from NHANES I. *Arch. Environ. Health* 46:135–144.
24. Schwartz, J. 1989. Lung function and chronic exposures to air pollution: a cross-sectional analysis of NHANES II. *Environ. Res.* 50:309–321.
25. Abbey, D. E., F. F. Petersen, P. K. Mills, and L. Kittle. 1993. Chronic respiratory disease associated with long term ambient concentrations of sulfates and other air pollutants. *J. Expo. Anal. Environ. Epidemiol.* 3:99–115.
26. Abbey, D. E. 1994. Incidence of respiratory symptoms and chronic disease in a non-smoking population as a function of long-term cumulative exposure to ambient air pollutants. *In* California Air Resources Board, Final Report. California Air Resources Board, Sacramento, CA. Publication No. A933-160.7.

APPENDIX

Additional Factors Evaluated for Confounding or Effect Modification

The factors evaluated for additional models were the following: whether father or mother had cancer; whether subject reported having high blood pressure at baseline; a physical exercise scale composed from a number of questions on leisure time and work physical activity and categorized as none, light, moderate, or heavy; whether subject currently used alcoholic beverages at baseline; times per week and dosage per week of antioxidant vitamins A, C, or E, as consumed in pills or multivitamin tablets; an index of magnesium intake; and times per week subject used cooked green vegetables, green salads, tomatoes, fruit or fruit juice, beans or lentils, and eggs. Various indices of meat, poultry, and fish consumption were also evaluated as well as years of the SDA lifestyle as measured by age at baptism into the SDA Church. Covariates that could modify exposure to ambient air pollutants or exacerbate health effects of such exposure were evaluated for interaction with the pollutant using the cross-product term of each such variable with the pollutant. Covariates evaluated for interaction included hours outdoors, computed as a weighted average of summer and winter seasons in 1977, antioxidant food intake as measured by the vegetable/fruit index; antioxidant vitamin index from supplements; fish consumption; and whether subject had heart attack, high blood pressure, stroke, or diabetes as reported at baseline. None of these showed significant interactions with PM_{10} or effect modifications in stratified analyses.

PM3006519108

Source: https://www.industrydocuments.ucsf.edu/docs/fngj0001